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Complex Regional Pain Syndrome

Michael Veltman
MBBS FANZCA FASE FFPMANZCA

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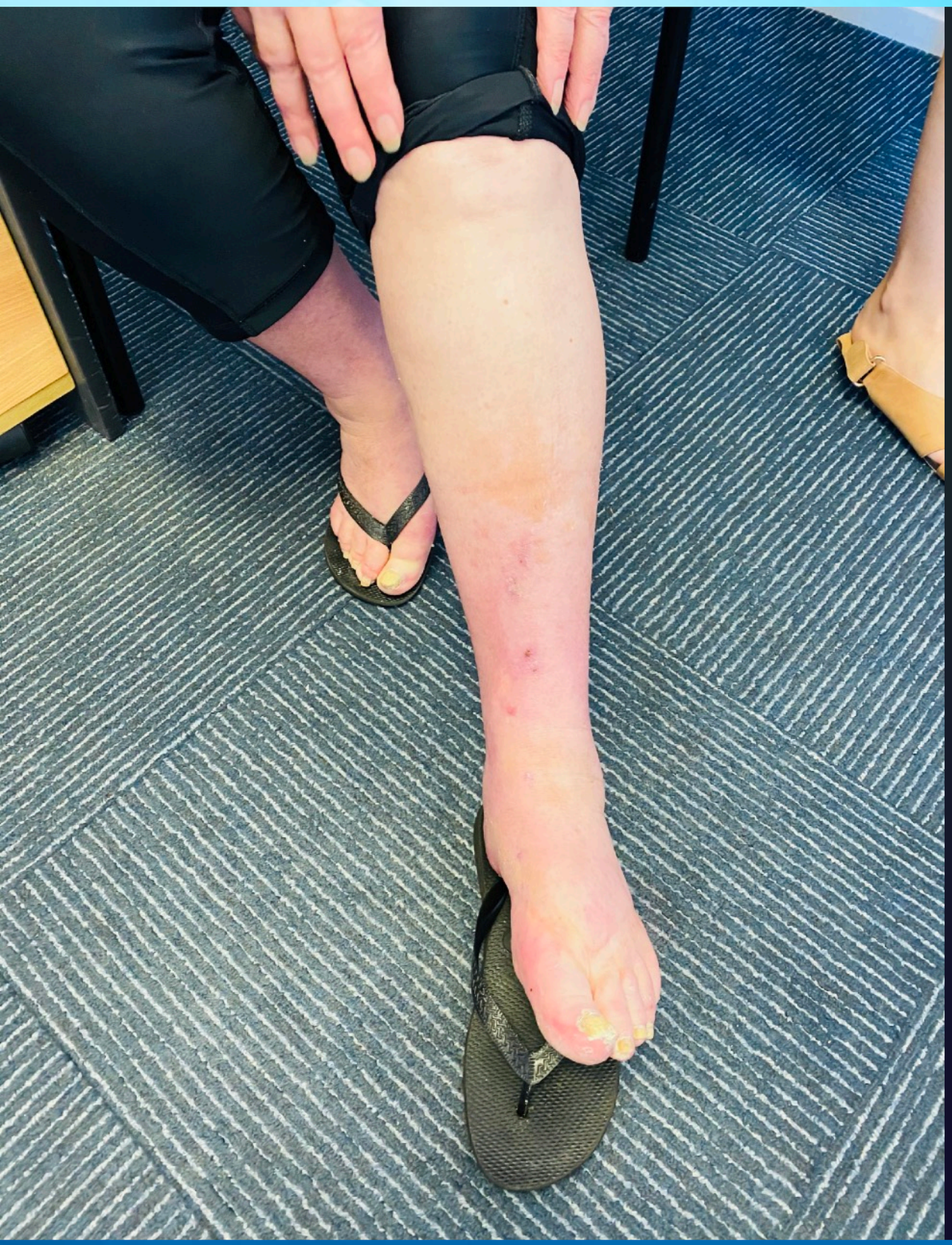

Outline

Definition

Diagnosis

Pathophysiology

Management

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What is CRPS

Lots of confusion about what this condition is:

"Reflex Sympathetic Dystrophy"

Multiple diagnostic criteria historically

IASP Budapest Criteria (1998) have the best acceptance.

Type I - With no nerve injury

Type II - With nerve injury

CRPS is a condition that should primarily be managed by pain specialists

Epidemiology

26.2 per 100 000 life years

c.f. RA 30/100 000, MS 4/100 000

Females 3.5:1

Upper limbs 60%

Type 1 most common

Increases with age - peak at 55 - 70 years

Economic Costs

Major costs to the community of CRPS

High levels of mobidity.

More pain and dysfunction than either rheumatoid arthritis or fibromyalgia.

Average health care costs were 5700 euros in 1998 - much higher now.

Inciting events

Peripheral musculoskeletal

- Fractures 45%
- Sprains 18%
- Elective surgery 12%

Nerve injury - Peripheral & Centeral

Other - CNS, Visceral

Idiopathic - 10%

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Other associated factors

Caucasian race

Higher median income

Depression

Drug abuse

Pre-existing pain conditions:

- Fibromyalgia
- Headache

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Protective factors

Associations with lower rates of CRPS

- Obesity
- Diabetes
- Hypothyroidism
- Anaemia

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Diagnosis

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Budapest Criteria

Consensus meeting in 2003

Improvement on previous IASP criteria

- Sensitivity 85%
- Specificity: 69%
  - 3 Symptoms
  - 2 Signs

IASP Clinical Budapest Criteria in diagnosing CRPS

1. Continuing pain that is disproportionate to any inciting event

2. At least one symptom reported in at least three of the following categories:

Sensory	Hyperesthesia or allodynia
Vasomotor	Temperature asymmetry, skin color changes, skin color asymmetry
Sudomotor	Edema, sweating changes, sweating asymmetry
Motor/trophic	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)

3. At least one sign at time of evaluation in at least two of the following categories:

Sensory	Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
Vasomotor	Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry
Sudomotor	Evidence of edema, sweating changes or sweating asymmetry
Motor/trophic	Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)

4. No other diagnosis can better explain the symptoms and signs

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Clinical Features

Negative Symptoms

Positive Symptoms

Autonomic Symptoms

Motor/trophic symptoms

Symptoms

Negative

- Hypoasthesia
- Sensory loss

Positive

- Burning pain
- Allodynia
- Hyperalgesia

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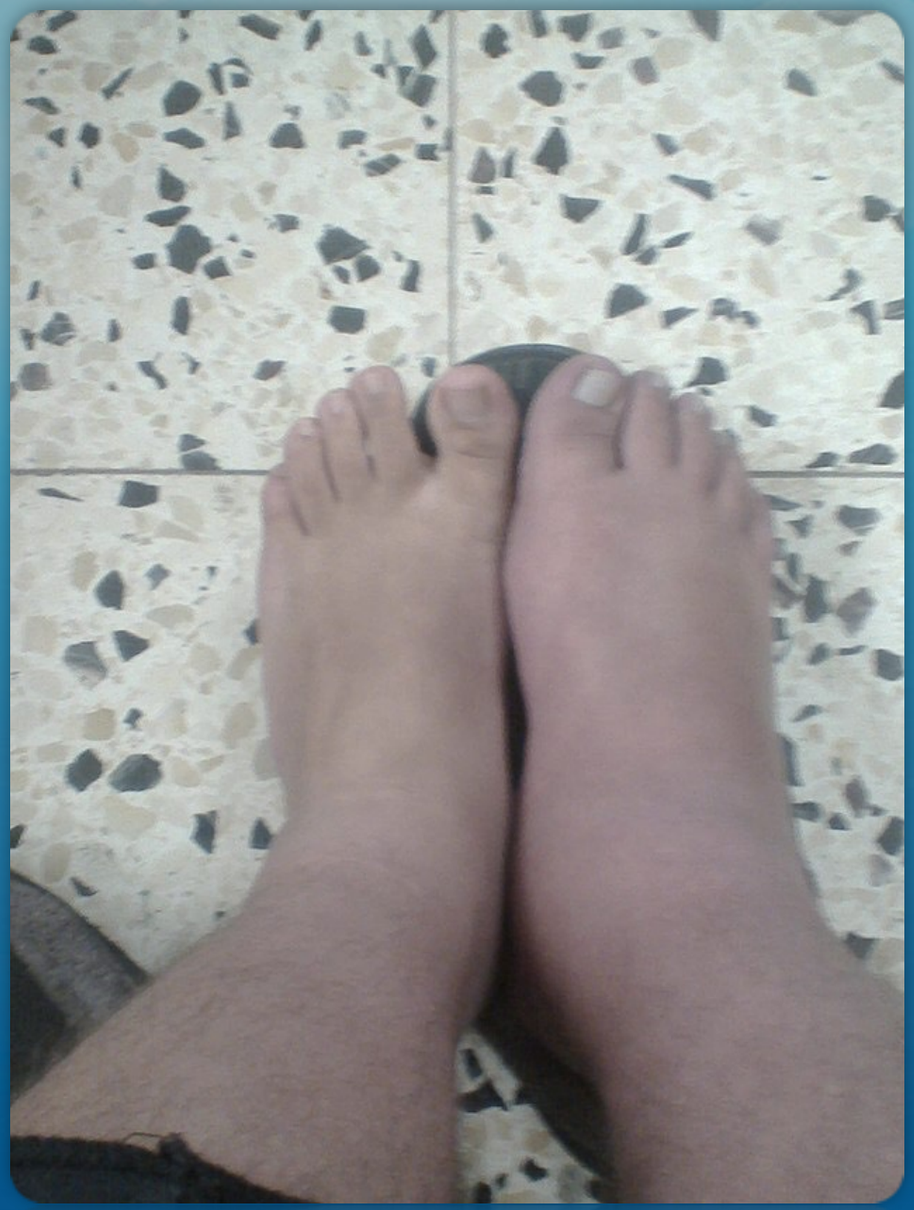
Vasomotor

- Temperature
- Colour



Sudomotor changes

Look for asymmetry of signs and symptoms of:

- Oedema
- Sweating

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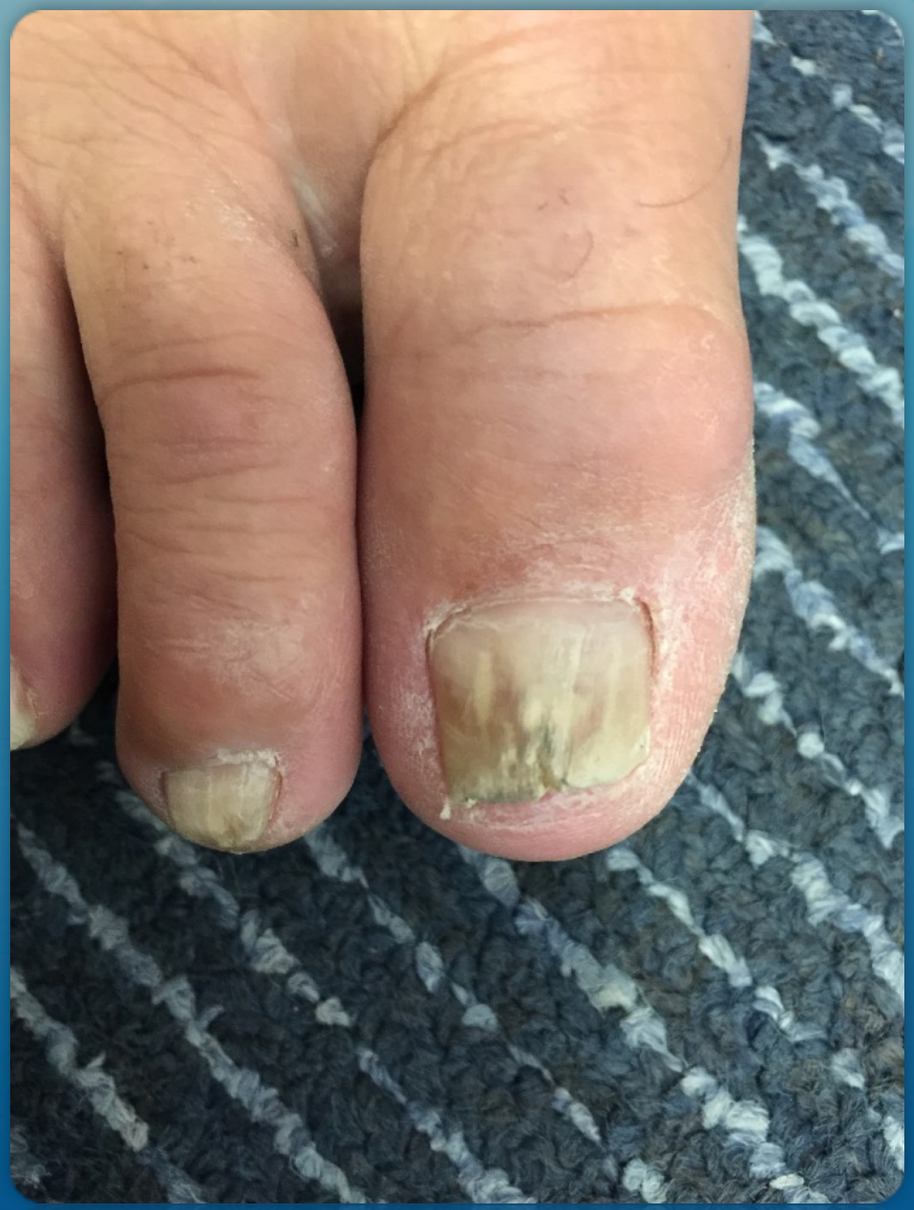

Motor/Trophic Symptoms

- Motor Changes
  - Weakness & Tremor
  - Reduced range of motion
  - Dystonia
- Trophic Changes
  - Hair & nail growth
  - Skin changes

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Key points in diagnosis

Use the Budapest criteria, but understand its limitations

Type I vs Type II CRPS is somewhat arbitrary.

Remember to exclude other conditions.

Generally only affects one limb

- But it can spread

Don't need to wait 3 months - and you shouldn't

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Pathophysiology

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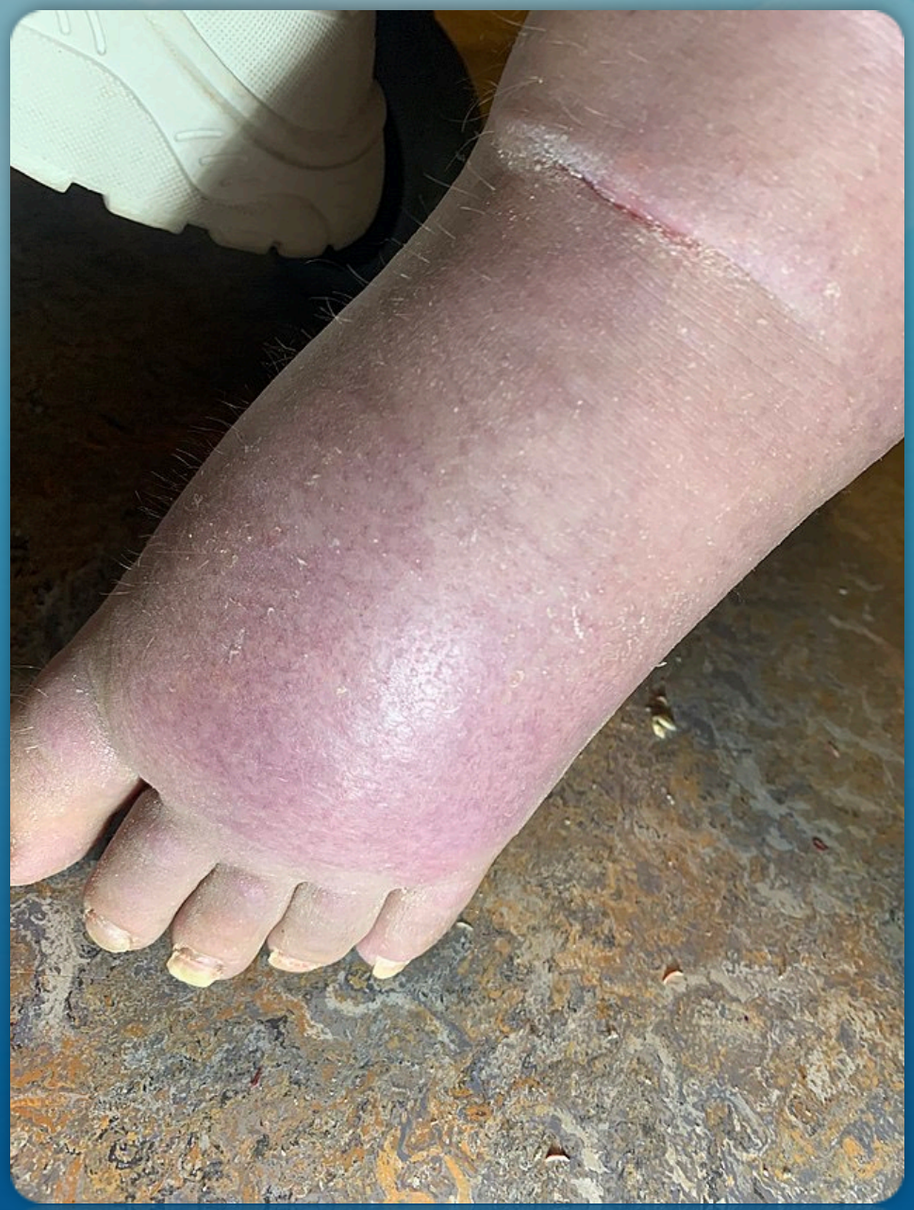

Pathophysiology

Inflammation

Sympathetic dysfunction

Autoimmune

Central Sensitisation

Limb Ischaemia

Cortical Reorganisation

Nerve Damage

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Inflammation

Pro-inflammatory immune response

Proliferation of keratinocytes and release of:

IL-6, IL-1β, TNF-α;

Histamine (warm phase)

Activation of osteoblasts and osteoclasts

Antigen mediated T cell response

Increased IL-10, decreased IL-37

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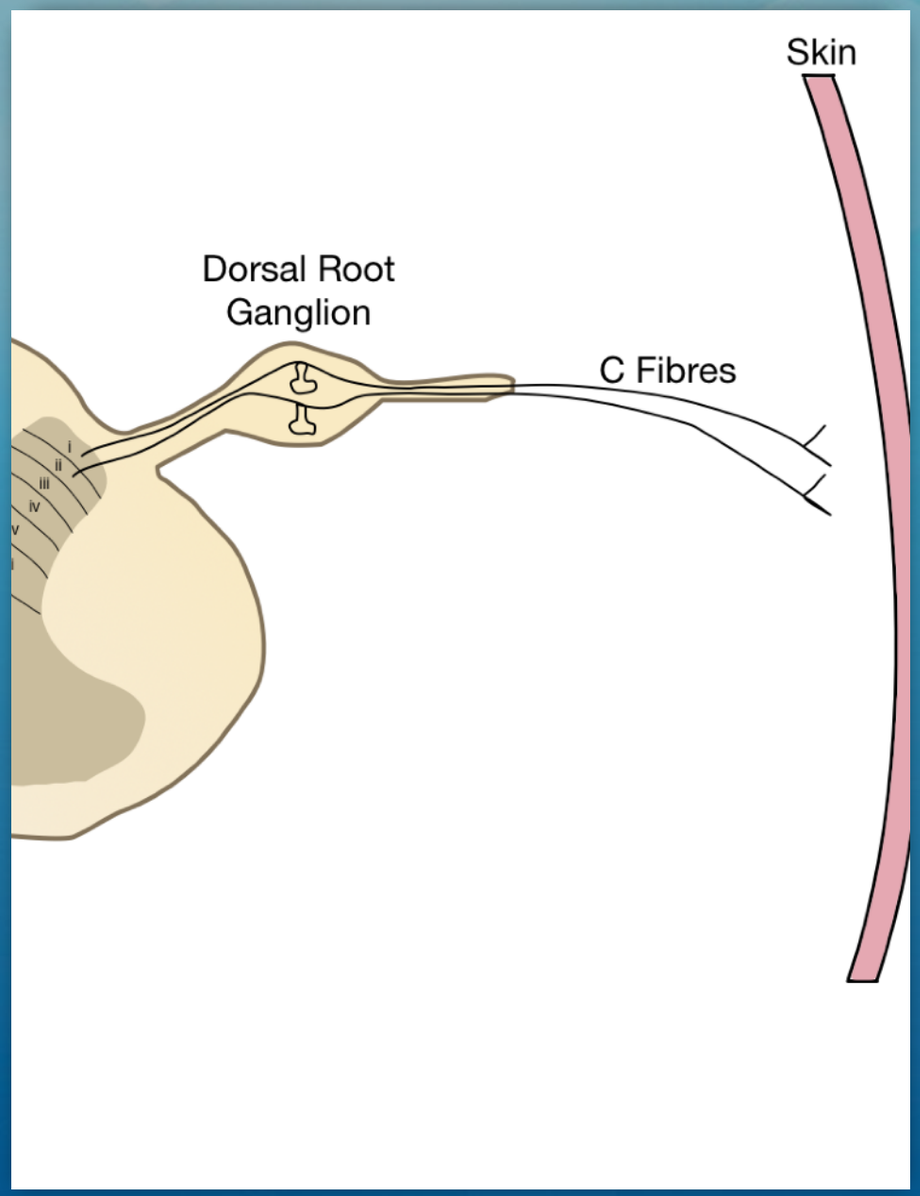


Inflammation & Pain Fibres

C-fibre activation

Afferent pain signals

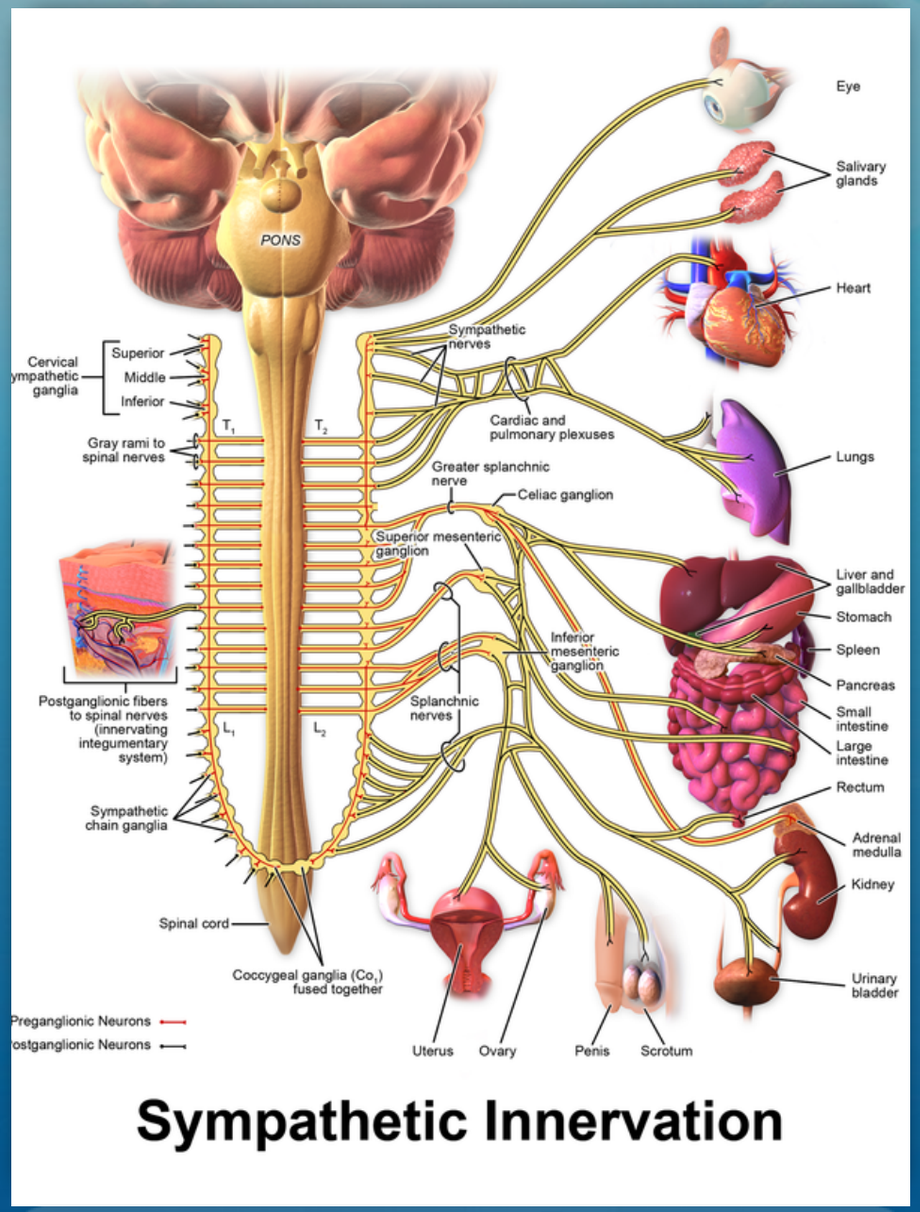
Efferent neuropeptides

CGRP, Substance P

Keratinocyte proliferation

A-α nerve fibre degeneration

A-δ nerve fibres preserved



Sympathetic Innervation

Autonomic Nervous System

Acute Phase

Reduced sympathetic activity

Up regulation of α_1 adrenergic receptors

Increased pain with α_1 agonists

Chronic Phase

Increased sympathetic activity

Increased cytokines

endothelin-1

noradrenaline

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Autoimmune Changes

Elevated autoantibodies in serum - IgG, IgM

Pain levels are proportionate to elevations in IgG

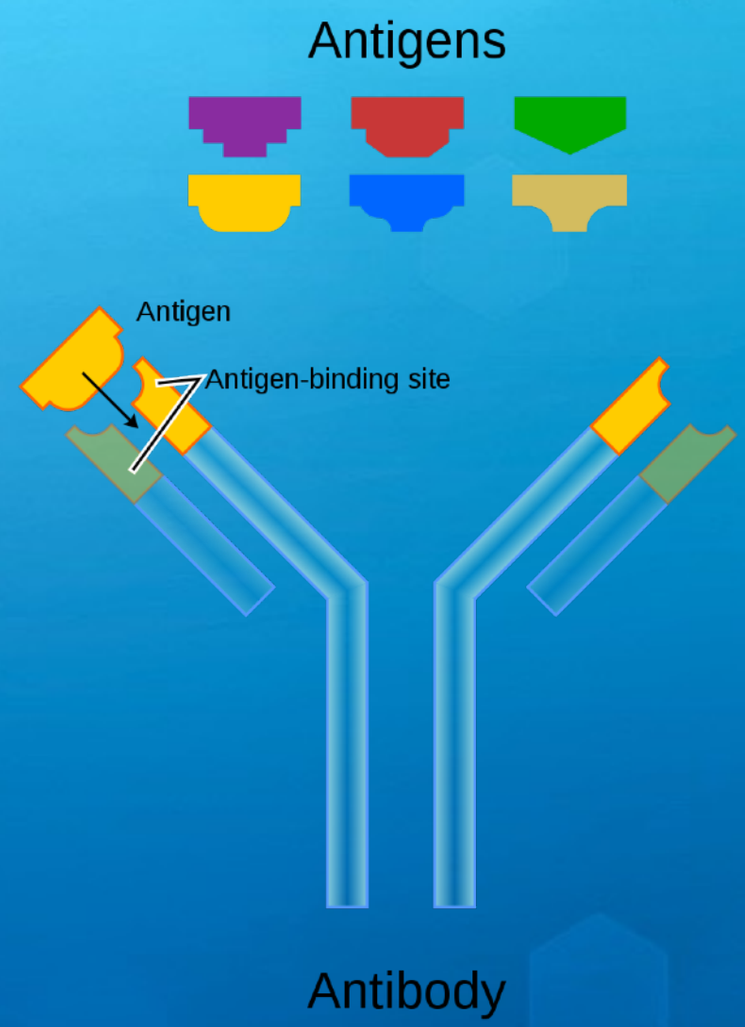
Antibodies have α_1, β_2 Adrenergic & M_2 Muscarinic agonist activity

IgM autoantibodies produce pain via

Direct action on targets

Complement activation

Deposition of antibodies



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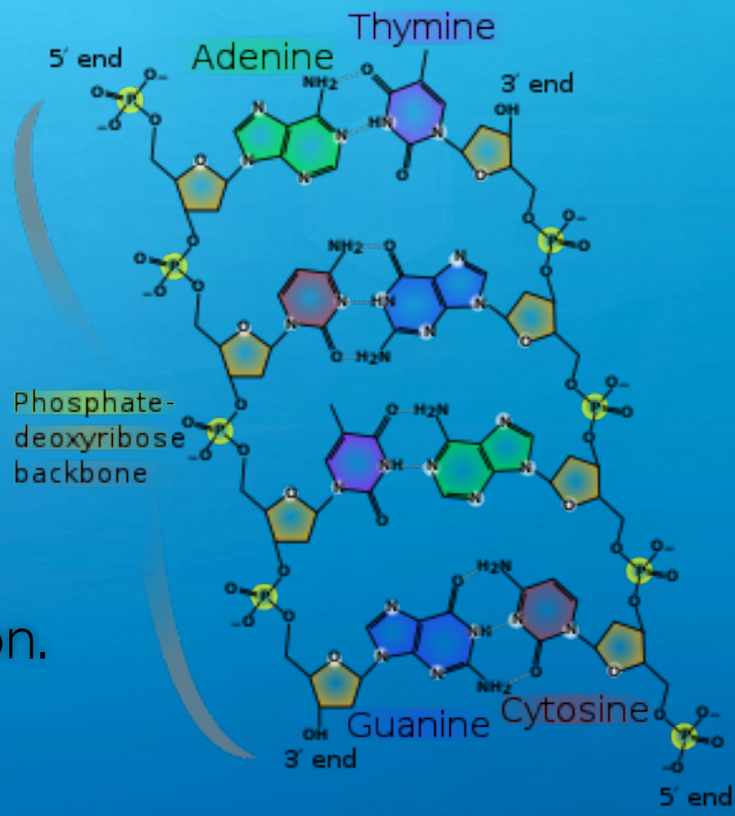
Genetics

Tends to run within families

- HLA DRB1 unregulated, HLA-DQB1 downregulated
- Other HLA associations: DQ1, DQ8, DR6, DR13, B62
- Role of HLA is to present antigens.



Epigenetic modification of CpG sites

- Mostly hypomethylation of sites related to immune function.

Genetic associations:

- β2 adrenoceptor polymorphisms, TNFα polymorphism

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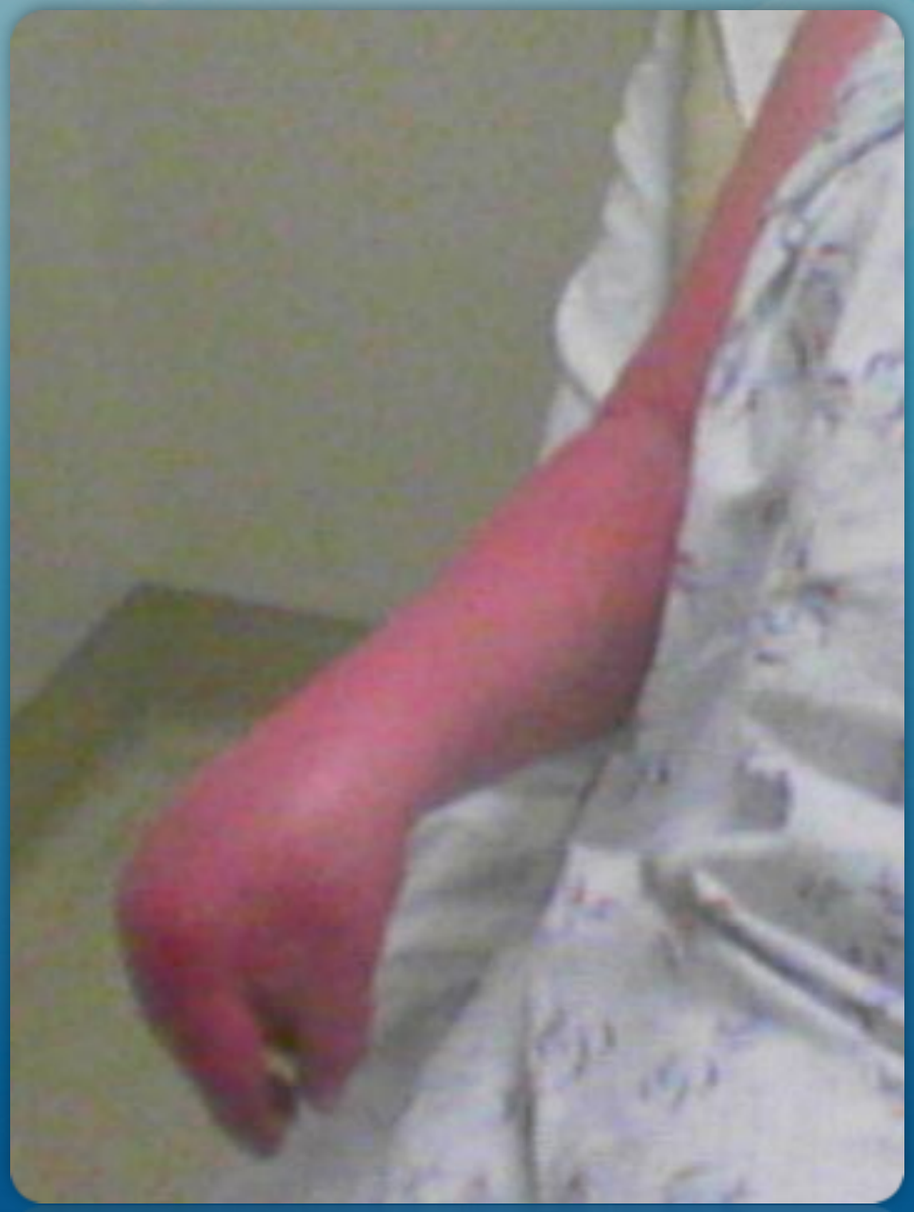
Clinical Course



Clinical Course

Three broad phases

- Warm (Acute inflammatory) phase
- Cold (Chronic inflammatory) phase
- Trophic phase - Probably an extension of the cold phase

Only 2% have relapsing/remitting phase

Phases aren't always present

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Clinical course

At 6 years after disease onset

30% of patients completely recovered

54% stable disease.

15% no improvement

Overall 30% of those who worked previously remain unable to work.

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Investigations

Limited value in CRPS

X-ray

Bony excavations, resorption, demineralisation

MRI

Effusions, marrow oedema

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Treatment Options

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Multidisciplinary Team

Physiotherapy / Occupational Therapy

- Mirror box therapy
- Graded Motor Therapy
- Desensitisation

Clinical Psychology

- CBT & ACT

Pharmacotherapy

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Non steroidal anti-inflammatory drugs

Traditional treatment, but actually little evidence

Non significant reduction of CRPS 500mg aspirin daily in one study.

Steroids

Prednisolone has some evidence.

Exact dose and duration not well established.

One study with benefit: 60mg daily for 28 days for acute phase

Superior to NSAID's

Not beneficial in chronic phase

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Antioxidants

Vitamin C - 500mg/day for 45-50 days

- Some evidence for dose of 500-1000mg /day most effective

Less evidence for

- Fish oil
- NAC 600mg/day
- Dimethylsulphoxide (DMSO) cream

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Biphosphonates

Several studies show benefit

Modulate inflammatory mediator, migration of marrow cells.

Palmidronate 60mg IV equal effectiveness as prednisolone

Antineuropathic agents

Effectiveness is unclear, but some studies show benefit.

- Gabapentin up to 1800mg/day
- Similar results shown for amitriptyline in some studies

Standard neuropathic treatment options probably apply here

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Limited evidence for some agents

Ketamine:

- Some evidence for intravenous and topical ketamine
  - No large RCT studies to date

Naltrexone - limited evidence for CRPS

Botox - significant reduction in pain in refractory CRPS

Plasma exchange therapy

CBD - reduction in pain scores in one study.

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Lacking Evidence

Capsacin

IT baclofen

IV Local anaesthetic

Pregabalin

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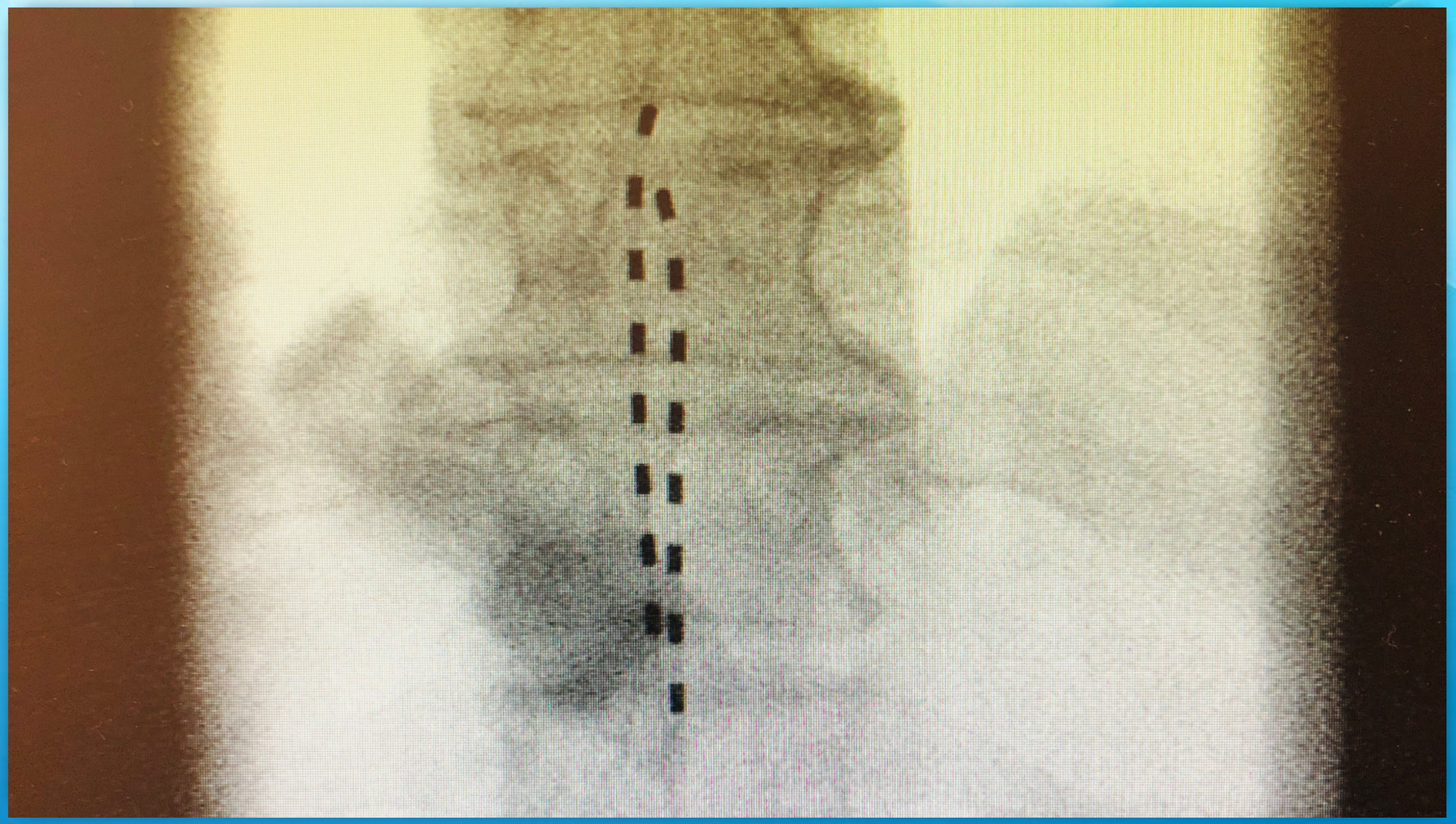

Neuromodulation

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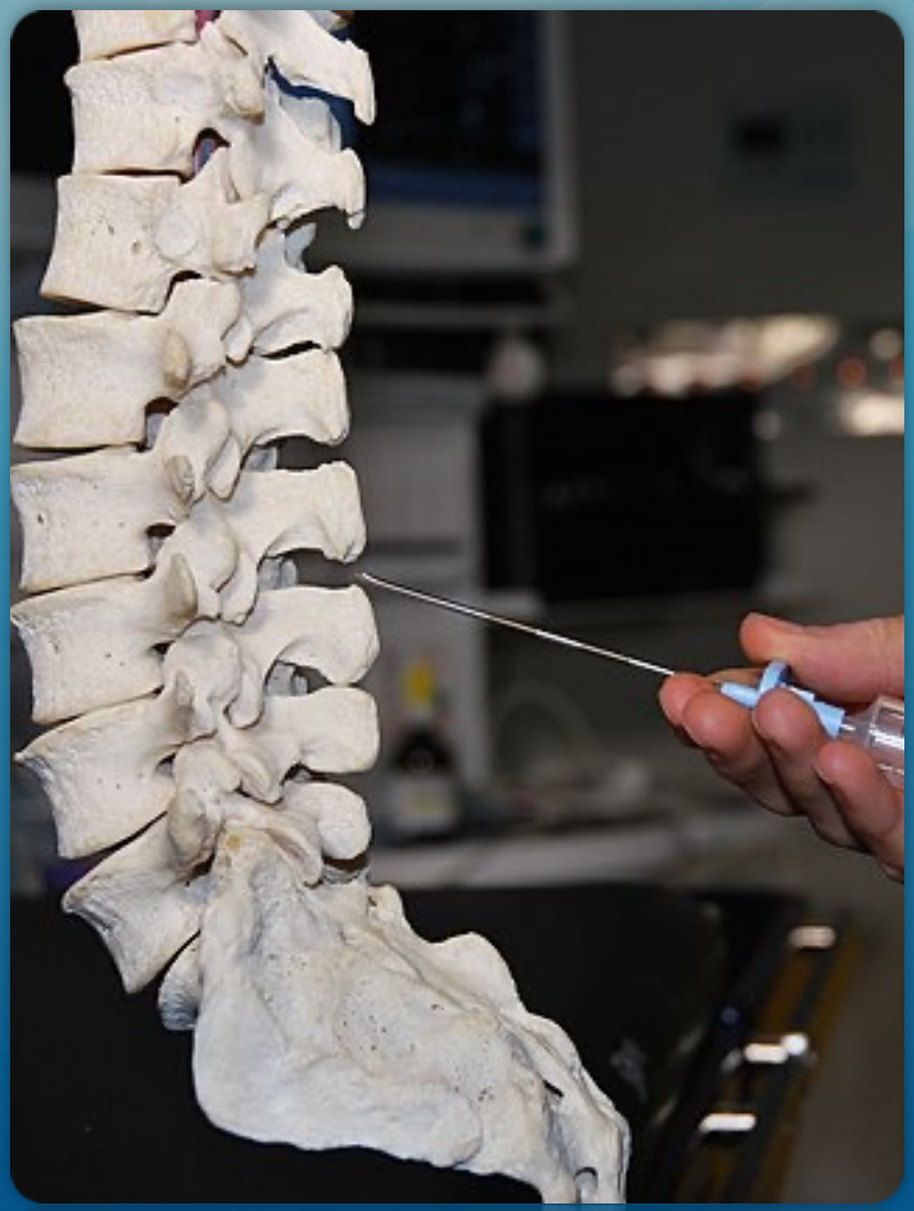
Transcranial Magnetic Stimulation

Magnetic pulses to induce cortical stimulation

Evidence that it reduces pain

Effect persists beyond duration of treatment.

Limited evidence to date.



Epidural blockade

Some evidence for sympathetic blockade at level of pain.

Most get pain reduction at time of procedure. Most get 1-4 weeks of benefit, a small number get persistent benefit

Stellate ganglion block may be of benefit for similar reasons

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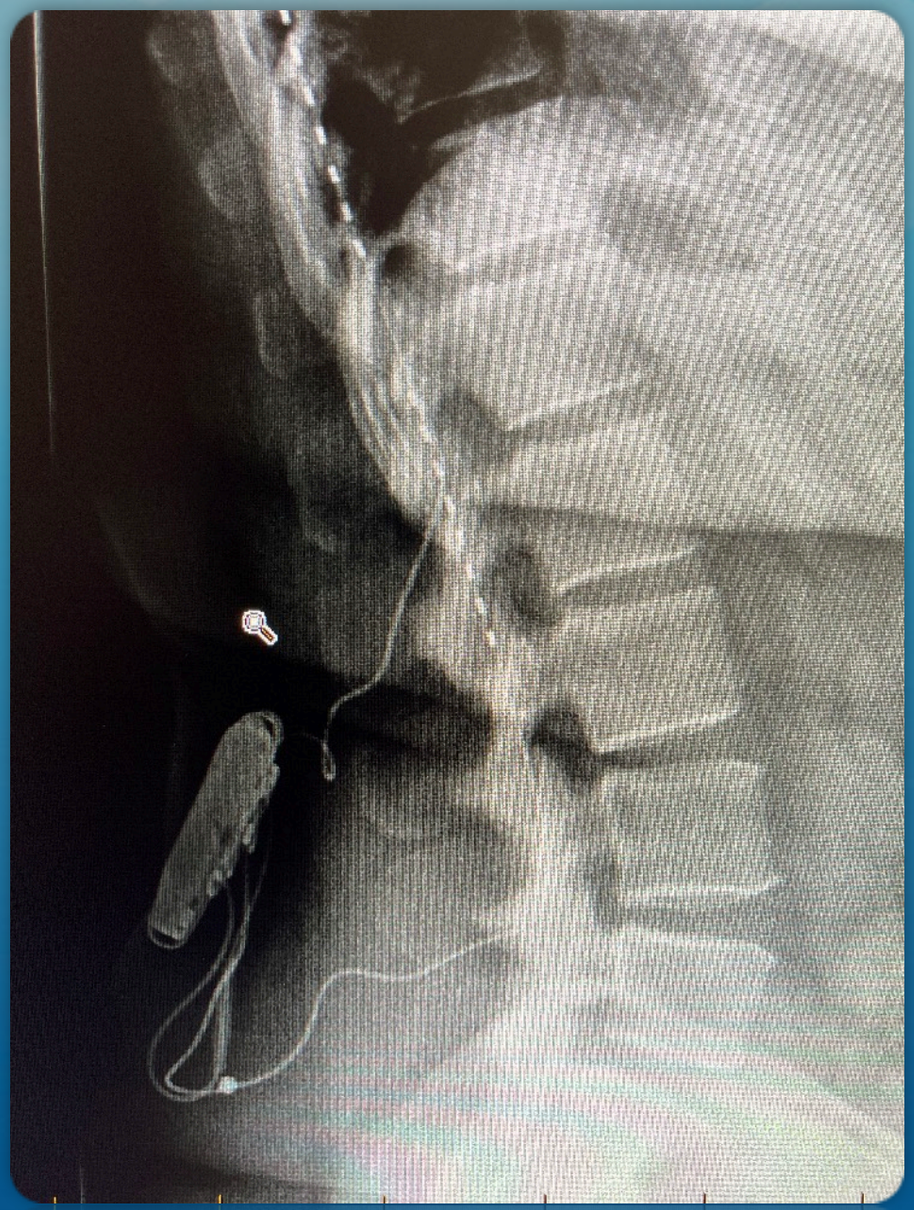

Neuromodulation

Spinal Cord Stimulation

Benefit seen for CRPS

Now getting >80% reduction in pain for most patients

Still some question about longer term efficacy.

Other interventions

Physiotherapy - Esp for upper limb

SCRAMBLER - May have some benefit

TENS - No evidence

OT - Some benefit

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Surgery

Sympathectomy

Some evidence for pain benefit

Amputation

No evidence.

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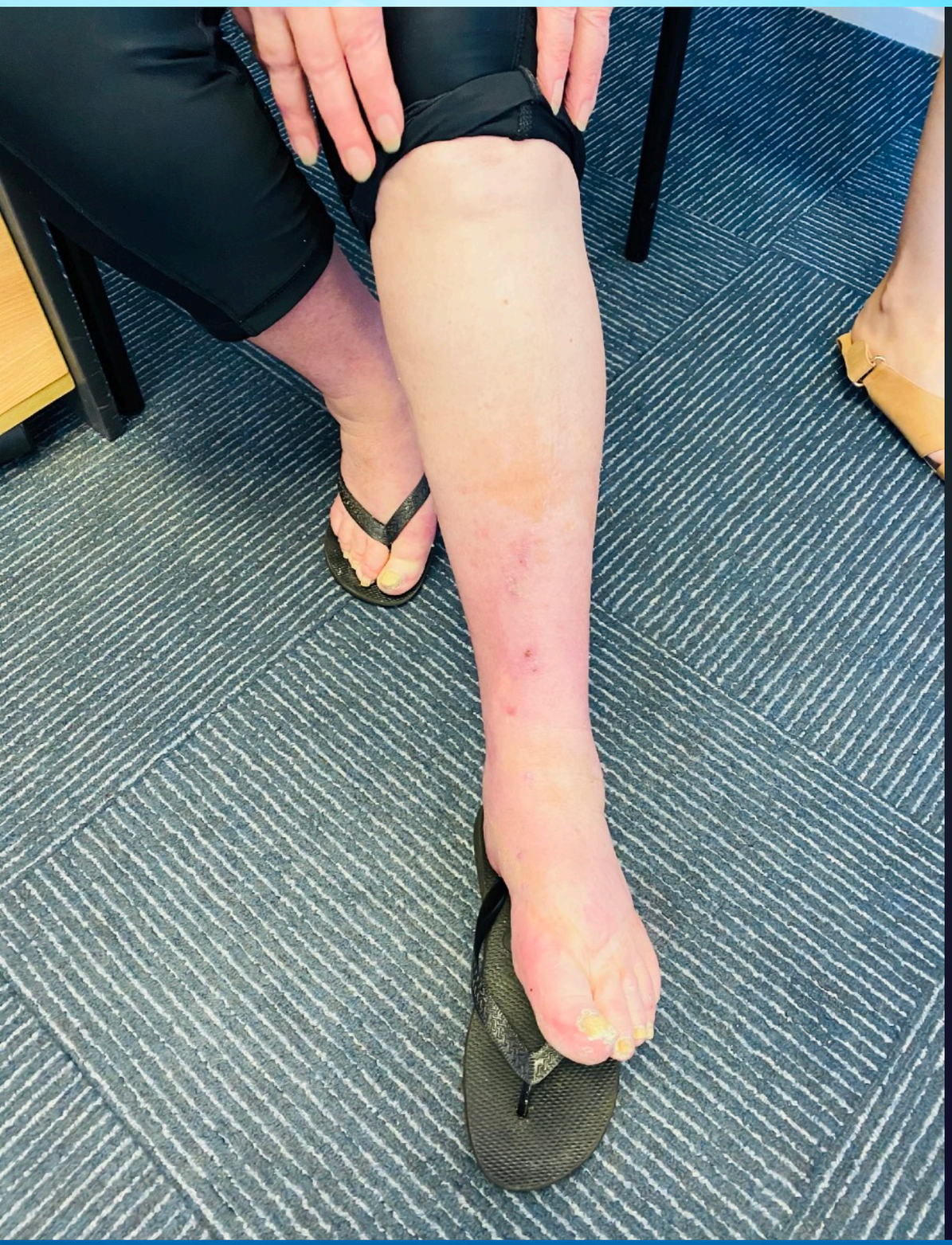

Summary

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